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09/889,251	11/01/2001	Robert K. Naviaux	UCSD1140-1	9760

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EXAMINER	
SPIVACK, PHYLLIS G	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,251	NAVIAUX, ROBERT K.	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A Request for Continued Examination (RCE) is acknowledged and accepted. A Preliminary Amendment filed June 18, 2004 is further acknowledged. All previous claims are canceled. New claims 67-94 are presented and represent all of the claims now under consideration.

An Information disclosure Statement filed June 18, 2004 is acknowledged and has been reviewed.

Claims 67-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The specification fails to disclose the subject matter of the present claims with respect to the recited compounds. In re Rasmussen, 211 USPQ 323. There is no support for the 2,4-diketone pyrimidines presently claimed. On pages 2 and 5 of the specification, R_1 in Formula I does not allow an oxo group. Further, R_3, R_4 and R_5 may not all be hydrogen. Accordingly, the compound depicted as Formula I in claims 67 and 91, as well as uridine and 1-β-D-ribofuranosyluracil, do not find support in the specification.

Claims 67-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to the treatment of any mitochondrial disorder, or for reducing or eliminating one or more symptoms associated with a mitochondrial disorder comprising administering the compound depicted as

Formula I, uridine or 1-β-D-ribofuranosyluracil. The specification provides support in Examples 1-4 on pages 14-19 for the treatment of mitochondrial renal tubular acidosis, Leigh syndrome, lactic academia, complex I deficiency, complex IV deficiency, MARIAHS syndrome and multiple mitochondrial deletion syndrome comprising administering triacetyluridine.

Attention is directed to In re Wands, 8 USPQ2d 1400 where the court set forth factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to treatment of any mitochondrial disorder comprising administering the compound depicted as Formula I, uridine or 1-β-D-ribofuranosyluracil.

The relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in mitochondrial pathology.

Each particular mitochondrial disorder has its own specific characteristics and etiology. The broad recitation "treating a mitochondrial disorder or reducing or eliminating one or more symptoms associated with a mitochondrial disorder" is inclusive of many conditions that presently have no established successful therapies.

It is clear the art to which the present invention relates is highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy.

The breadth of the claims

The claims are very broad and inclusive of any mitochondrial disorder.

The amount of direction or guidance provided and the presence or absence of working examples

The working examples are limited to the administration of triacetyluridine.

The quantity of experimentation necessary

Applicants have failed to provide guidance as to which particular compound among the compound depicted as Formula I, uridine or 1-β-D-ribofuranosyluracil would be preferred for treatment of the which particular mitochondrial disorder. The skilled artisan would expect the interaction of a particular agent in the treatment of a particular

mitochondrial disorder to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for each agent. The instant specification sets forth no such understanding or any criteria for extrapolating beyond the administration of triacetyluridine. Even for the Examples presented, no direction is provided to treat any other disorder beyond mitochondrial renal tubular acidosis, Leigh syndrome, lactic academia, complex I deficiency, complex IV deficiency and MARIAHS syndrome. Absent reasonable *a priori* expectations of success for using a particular pyrimidine to treat any particular mitochondrial disorder, one skilled in the art would have to test extensively many compounds to discover which particular disorder responds to that particular pyrimidine. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 68 and 92 are rejected under 35 U.S.C. 102(a) as being anticipated by Loffler et al., Cell. Biochem.

Loffler broadly discloses uridine treatment for patient suffering from mitochondrial disorders. See the end of the second column on page 128.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 67-80 and 88-94 are rejected under 35 U.S.C. 103(a) as being unpatentable over von Borstel, R.W., U.S. Patent 6,472,378.

Von Borstel teaches the administration of uridine or pyrimidine nucleotides and precursors to treat mitochondrial disorders. See column 4, lines 48-61. The reference does not point out the specific compound of Formula I or 1-β-D-ribofuranosyluracil. However, these compounds are encompassed in the recitation "pyrimidine nucleotide precursors" or nucleotides of pyrimidine. Therefore, in view of von Borstel's teaching, one skilled in the art would seek such pyrimidine nucleotide precursors or nucleotides of pyrimidine with a reasonable expectation of treating various mitochondrial disorders. The determination of an optimal dosage is a parameter well within the purview of those skilled in the art through no more than routine experimentation.

No claim is allowed.

Any inquiry concerning this communication should be directed to Phyllis G. Spivack at telephone number 571-272-0585.

Phyllis Spivack

Phyllis G. Spivack
Primary Examiner
Art Unit 1614

September 4, 2004

PHYLLIS SPIVACK
PRIMARY EXAMINER